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Mood In Relationship To Immuno-competence And Physical Illnesses

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Two groups were evaluated in terms of measures of their mood, immune system and endocrine stress: cyclothymic subjects in depressed and euthymic states (Study 1) and patients with major depression at intake, termination and follow-up with dynamic psychotherapy (Study 2). These physically healthy young adults generally did not show mood-related impairments in terms of immune system measures. The ACTH measure was more related to immune decrements than the depression measures.

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FINAL REPORT ONR CONTRACT #N0014-87-K-0498
August 2, 1990

PRINCIPAL INVESTIGATOR: Dr. Lester Luborsky*
CONTRACTOR: University of Pennsyvlania

CONTRACT TITLE: MOOD IN RELATION TO IMMUNOCOMPETENCE

START DATE: OCT. 1987

RESEARCH OBJECTIVE: The study had two main aims: 1) to examine the degree of association of measures of mood and stress with measures of immunocompetence; 2) to examine endocrine stress measures as a possible mediating link between mood, stress and immunocompetence.

Study 1

This study was designed to evaluate the association of mood and immune measures in normal subjects who had extreme shifts in mood.

Subjects: During the past three years we have studied a group of cyclothymic subjects (Group 1). These are normal subjects who have extreme fluctuations in mood sufficient to fit the category of cyclothymia. The screening instrument for selecting subjects was the "General Behavior Inventory" (Dupue et al., 1985) which is a reliable questionnaire for detecting fluctuations in mood. All of these subjects are medication-free so that measures of immune functioning would not be interfered with.

Measures: Thirteen of these subjects were evaluated at two times: when their mood was euthymic and when they were depressed. At both times they were given assessments of mood and stress which included the Beck Depression Inventory (BDI), The Hamilton Depression Rating Scale (observer-rated) and the Symptom Checklist-90 (abbreviated). Seventeen immunocompetence measures assessed from the same blood samples are listed in Table 1. Because of the large number of measures in relation to the number of subjects, our conservative strategy was to focus on the few immune measures that were most related in other studies to standard measures of depression and stress (based on the review by Luborsky et al., in preparation). These immune measures were natural killer cells (NK: Leu 4+9+; NK: Leu 2+7+) and antibody measures (EBV, HSV). The hypotheses based on this review (and others like it, such as Evans, 1988) were that

*With the collaboration of Jacques Barber, Michael Prystowsky, Arnold Levinson, Eva Redei, John Cacciola, Paul Crits-Christoph, George Flickenger (and Ronald Gleser for the antibody measures)

NK measures would decrease with greater depression and stress and that antibodies would increase with greater depression and stress.

Results: As shown, in Table 1 the patients differed significantly in their level of depression (BDI's and Hamilton Depression Rating Scale (total)) in the two states. The immunocompetence measures in the two states, however, did not differ significantly. We also examined the correlations of change in BDI with change in immune functioning (Table 2a); these correlations were also not generally significant.

Study 2

The second study was designed to investigate the association of mood shifts and immune measures in depressed patients as well as to examine their relation to endocrine stress measures.

Subjects: Group 2 consisted of patients who were diagnosed as DSM-III major depression-unipolar according to the SADS-RDC. These patients were also medication free. They were given time-limited (16 sessions) dynamic psychotherapy guided by the supportive-expressive psychotherapy manual (Luborsky, 1984). They were assessed before treatment, at the end of the treatment (4 months) and again six months later. A battery of immune measures and endocrine stress measures were assessed at the three points. The endocrine stress measures were from blood samples and included plasma cortisol, ACTH and plasma beta-endorphin. The same 17 immune measures were measured as in Group 1, but with the addition of two antibody measures: Herpes Simplex virus (HSV) & Epstein-Barr virus (EBV).

Results:

In the results that follow we especially examined immune measures as correlates of the therapy-induced relatively large change in depression from intake to termination. In addition, we have given some attention to the smaller change, from termination to follow-up.

Levels of depression
in relation to psychotherapy:

Because these patients were provided with psychotherapy for their depression we expected them to show decreases in depression from the beginning to termination and a slight further decrease or a stabilization during the six months follow-up period. In fact, they did show significantly large decreases in depression, during psychotherapy, as measured by the BDI and by the Hamilton Depression Scale (see Table 3). (They also showed decreases in anxiety and

in general level of severity on the Symptom Checklist) While the patients were all severely depressed before treatment, at the end of treatment two-thirds of them were moderately to much improved; a high percentage of these remained at this level during follow-up six months later.

Levels of endocrine stress in relation to psychotherapy:

There is no research evidence about the way these endocrine stress measures change in relation to psychotherapy; our expectation was that they would decrease, at least slightly. For ACTH & Cortisol, they are essentially unchanged (Table 7); for the Beta-endorphins there were slight increases.

Levels of the immune measures in relation to psychotherapy:

There are only a few significant differences in the immune measures between the intake and termination points (Table 4). All five measures (out of 19) that are significant are in the expected direction of a larger percent positive or larger mean absolute number.

It is noteworthy that the NK measures show the pattern expected according to the hypothesis -- the mean absolute numbers of these cells increased during treatment (which had significantly reduced the depression). That was one of the main hypotheses in relation to changes during treatment. But surprisingly the increase was lost during the six-month period after the treatment. During the follow-up period, we would have expected the increase to remain because the depression tended to remain low.

The significant changes in level from termination to follow-up were not expected (Table 5) -- nine of these variables showed significant <u>decreases</u> (at close to the .05 level or better) after the end of treatment.

Correlations of depression with immune measures at each assessment point:

On the basis of our initial review of studies on this topic (Luborsky et al., in preparation) we expected higher depression to be associated with lower immune measures. Our findings showed much less of this trend than we expected. In general, there were very few or no significant correlations at intake, termination or follow-up. As Table 6 shows there were only three that nearly reached the .05 level at intake and only one at termination and one at

follow-up and none of the measures were the same ones at the three points. Because of restriction of range we expected higher correlations at termination where we had both remitted and nonimproved patients.

Correlations of endocrine stress measures with immune measures at each time*

ACTH:

There were several significant correlations of ACTH with the 19 immune measures (Table 8). The most impressive of these is T cell CD8 which showed a significant correlation at all three time points. The correlations that were significant tended to be in the expected direction, that is, the higher the ACTH the lower the immune measure.

Cortisol:

Several of these 19 correlations were significant in the expected direction (Table 8). The most impressive of these is helper-inducer Leu 3+18- with a correlation of -.56 for percent positive, significant at $p < .005$ at before treatment.

Beta-endorphins:

The few of these 19 correlations (Table 8) that were significant were in the expected direction.

Correlation of change in depression with change in immune measures:

The correlations with change in mood on the BDI with change in immune measures partialing out initial levels showed only a few that were significant and the size of the correlations was modest (Table 9). In view of the large number of correlations performed it is not possible to make any clear inferences about the particular measures that were significant - of the 19 correlations, only two were significant (at the .05 level).

Correlation of change in endocrine stress measures with change in immune measures:

*The assays for the ACTH & Cortisol measures were redone on another portion of the same samples by a more sensitive method (under the supervision of Dr. Eva Redei). The results were essentially nonsigrificant.

Changes in endocrine stress measures showed a trend to be related negatively with changes in immune measures (Table 10). Changes in ACTH, for example, from intake to termination, are correlated -.65 with changes in T cell CD2 -- this means that when ACTH decreases then T cells increase. The direction of the correlation is what would be expected from a long line of studies, mostly with animals, relating endocrine stress measures to immune measures ( ).

Conclusions

The main conclusion is that these physically healthy young adults, either with cyclothymic mood variations or with long lasting depression, generally did not show related major impairments in terms of immune measures. The most telling findings from our data that led to this conclusion were the following:

For the cyclothymic subjects (Study 1) the immune measures did not show significant differences between a depressed and a euthymic (normal) state.

For depressed patients (Study 2), although they markedly reduced their depression from before psychotherapy to the termination 4 months later and to follow-up 6 months after that, nevertheless: (1) their immune measures usually did not show significant change in level at the three points (NK measures are an exception) (2) within each of the three assessment points, their depression measures were not significantly correlated with their immune measures in the expected direction -- higher depression scores were not generally associated with lower scores on the immune measures.

Another analysis that bears on the relation between depression and immune measures is the correlation of <u>change</u> in depression to <u>change</u> in immune measures (Table 5). These analyses also do not usually show significant correlations.

A second conclusion, for which there is only modest support, is that the endocrine stress measures are more related to immune decrements than depression is related to immune decrements. The primary evidence came from the correlations of ACTH with the immune measures.

<u>Factors that may influence these results</u>:

It is important to note the breadth of the sample of immune measures -- they were not limited to phenotypic markers. In fact, the main trend in our results also appeared with the two functional antibody measures (EBV & HSV) of the kind used by Gleser et al. (1985) and these two antibody measures were even assayed by Gleser's staff. These two measures did not show any significant correlations

with the immune measures nor with changes in them over the three points in time.

A serious possibility that also needs to be considered is that the dysfunctions of the immune system that are reported to be associated with depression (Luborsky et al., in preparation) mainly exist when the patients are much more acutely stressed (and perhaps also much more depressed) than was true for our patients. Many of the studies which found this relation, such as some by Kiecolt-Gleser and their group (1986), assessed medical students before their examinations -- an example of an acute stress condition and not of chronic depression. In contrast, the patients in our sample have almost all been depressed for months, or even years and their endocrine stress levels may have shown adaptation.

To be able to examine this possibility we had included assessments of endocrine stress measures at the three points. The verdict from these measures was that the stress levels were not high and that the levels did not change significantly at the three points. Therefore, the mostly nonsignificant relations between depression and immune measures could be a function of the low endocrine stress levels and their small changes over time, which may be the result of adaptation to chronic stress.*

*Acute stress may be associated with decreased immune responsiveness in animal studies (Rabin et al., 1990). But the same study points out that habituation may explain the lack of stress-induced immune deficiencies reported by others.

References

Depue, R., Kleiman, R.,* Davis, P., Hutchinson, M., & Krauss, S. (1985) The behavioral high-risk paradigm and bipolar affective disorder, VIII: Scram-free cortisol in non-patient cyclothymic subjects selected by the General Behavior Inventory. American Journal of Psychiatry, 142, 175-181.

Evans, D. (1988). Depression and aging: Psychoneuroendocrinology and psychoneuroimmunology. Progress in NeuroEndocrinImmunology, 1, 21-27.

Glaser, R., Kiecolt-Glaser, J., Genge, J., Speicher, C. & Holliday, J. (1985) Stress, loneliness and changes in herpes-virus latency. Journal of Behavioral Medicine, 8, 249-260.

Kiecolt-Glaser, J., Glaser, R., Strain, E., Stout, J., Tarr, K., Holliday, J., & Speicher, C. (1986) Modulation of cellular immunity in medical students. Journal of Behavioral Medicine, 9, 5-21.

Luborsky, L., Houldin, A., Prystowsky, M., Levinson, A., Crits-Christoph, P., Barber, J., Schaffler, P & Stibbe, J. (in preparation). Mood, stress & immunocompetence - A review of their association.

Rabin, B., Cunnick, J., Lysle, D. (1990) Stress-induced alteration of immune function Progress in NeuroEndocrinImmunology, 3, 116-124.

Table 1
Immunocompetence of Depressed vs. Euthymic Students
(Group 1)

MEASURE	DEPRESSED		EUTHYMIC		t	p
TCELLCD2	1334.17	500.92	1459.17	424.57	-.80	.44
TCELLCD3	1188.18	470.23	1290.00	352.19	-.70	.50
TCELLCD4	677.50	258.95	735.83	202.60	-.87	.40
TCELLCD8	515.83	203.22	592.50	213.68	-1.03	.33
LEU3+8-	472.50	334.15	494.17	250.80	-.24	.81
LEU3+18+	340.83	226.37	389.17	242.84	-1.11	.29
NK:LEU4-19+	109.17	57.91	120.00	90.55	-.41	.69
&NK,LEU2+7+	126.36	171.54	172.73	157.93	-.62	.55
BCELLCD20	198.33	172.35	187.50	125.85	.23	.82
IL2R+CD3+	231.11	573.81	62.22	49.19	.86	.42
CD3+TRANS.REC.	211.00	541.45	60.00	65.15	.86	.41
LEU2+DR+	101.82	169.05	90.91	78.16	.17	.87
LEU5+DR+	130.83	272.18	103.33	85.00	.34	.74
LEU11	66.36	47.39	100.00	86.60	-.98	.35
CD4/CD8 ratio	1.38	0.40	1.28	0.35	1.01	.33
LEU3+8 ratio	1.48	0.88	2.97	4.54	-1.16	.27
LEU11C	4.29	2.95	5.36	3.85	-.77	.46
HAMTOT	12.71	4.28	2.21	1.97	9.19	.00
BDI	22.64	10.16	3.29	1.94	7.79	.00

Table 2
Significant Correlations between changes in BDI and changes in immune functioning across depressed and euthymic states (Group 1).

Variable	Part Corr	Partial	T	Sig T
T cell CD2	-.47	-.56	-1.90	.09
T cell CD3	-.50	-.58	-1.90	.10
T cell CD4	-.48	-.56	-1.92	.09
Helper cell	-.55	-.64	-2.37	.05

Table 3
Changes In Means On Depression And Anxiety Measures (Study 2)

A) From Intake to Termination

	INTAKE			TERMINATION			
	mean	SD	n	mean	SD	t	p
BDI	28.92	7.24	25	15.04	11.66	5.49	.000
HAM DEP	18.20	3.35	25	8.44	6.75	8.33	.000
SCL	141.60	43.35	25	73.56	58.90	6.47	.000
SCLANX	15.17	8.78	23	7.09	5.22	4.78	.000

B) From Termination to Follow-up

	TERMINATION			FOLLOW-UP			
	mean	SD	n	mean	SD	t	p
BDI	15.58	11.58	24	12.54	9.28	1.72	.099
HAMDEP	9.10	6.91	21	8.05	5.70	.7[illegible]	.486
SCL	79.81	59.45	21	73.00	46.50	.82	.424
SCLANX	8.24	4.92	17	7.94	5.80	.25	.807

Table 4
Immune measures with significant differences between intake and termination (Group 2)

Variable	Number of Cases	Intake Mean	SD	Term. Mean	SD	t	P 2-Tail
T cellCD3	24	68.13	6.97	70.21	8.10	-1.96	.06
T cellCD8	24	28.38	5.55	31.58	8.50	-2.00	.06
NK leu	24	5.92	2.95	8.79	5.51	-2.94	.01
TANDNK	24	7.38	5.06	9.67	6.67	-2.22	.04
NK leu: mean absolute	22	130.45	87.10	194.55	116.20	-2.60	.02

Table 5

Differences in immune measures between (Group 2) termination and follow-up

Variable	Number of Cases	Term. Mean	SD	Follow-up Mean	SD	t	P (2-Tail)
T cellCD8	24	31.58	8.50	28.71	6.01	-1.75	.09
CDRAT	24	1.45	.58	1.66	.52	1.87	.07
T cellCD2 mean absolute	23	1681.30	532.59	1406.96	563.50	-2.47	.02
T cellCD3 mean absolute	24	1560.83	504.23	1200.42	508.79	-3.67	.00
T cellC D8 mean absolute	24	701.67	273.09	535.83	237.96	-3.09	.01
Suppressor-inducer leu mean absolute	24	765.42	312.12	639.17	306.00	-2.07	.05
NKleu mean absolute	24	191.25	114.37	136.25	118.94	-2.94	.01
BCELL mean absolute	24	286.25	138.31	212.92	131.66	-1.97	.06
C11 mean absolute	18	163.33	136.98	112.22	127.07	-2.34	.03
Lymphocyte	22	33.86	7.27	29.41	9.02	-1.92	.07

Table 6

Correlations between Depression (BDI) and immune measures

AT INTAKE

Variable correlated with BDI	r	n	p
B cell CD20			
% positive	-.29	25	.083
mean absolute number	.34	23	.056
IL2R+CD3+	.28	25	.087
CD4/CD8 ratio	-.29	25	.077

AT TERMINATION

Variable correlated with BDI	r	n	p
Subset of T&NK cells leu3+18+	-.32	24	.062

AT FOLLOW-UP

Variable correlated with BDI	r	n	p
Suppressor Inducer leu 3+18+ mean absolute number	.30	24	.081

Table 7

Levels of Endocrine Stress Measures at Three Times (Group 2)

	Intake			Termination			Follow-up		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
ACTH	19.08	13.28		18.43	10.88		18.80	8.04	
Cortisol	12.8	5.13		12.08	6.60		11.79	4.11	
B-Endorphins	38.87	27.4		41.90	31.9		47.8	37.2	

Table 8

A. Significant Correlations of ACTH With Immune Measures (Group 2)

AT INTAKE Variable correlated with ACTH	r	n	p
% POSITIVE			
MEAN ABSOLUTE NUMBER			
T cell CD2	-.38	18	.060
T cell CD3	-.34	19	.076
T cell CD8	-.41	19	.042
Helper-Inducer leu 3+8-	-.36	18	.072
NK cells 4-19+	-.35	19	.073

AT TERMINATION Variable correlated with ACTH	r	n	p
% POSITIVE			
T cell CD2	-.42	19	.035
T cell CD8	-.34	20	.069
B cell CD20	.35	20	.066
CD4/CD8 ratio	.32	20	.088
MEAN ABSOLUTE NUMBER			
T cell CD8	-.35	20	.064

AT FOLLOW-UP Variable correlated with ACTH	r	n	p
% POSITIVE			
T cell CD8	-.44	21	.024
MEAN ABSOLUTE NUMBER			
T cell CD4	-.37	21	.049
T cell CD8	-.41	21	.032

Table 8 (continued)
B. Significant Corrleations Of Immune Variables With Cortisol

AT BEGINNING Variable correlated with Cortisol	r	n	p
% POSITIVE			
T cell CD4	-.35	21	.061
Helper Inducer leu 3+18-	-.56	20	.005
Suppressor Inducer leu 3+18+	-.40	21	.038
MEAN ABSOLUTE NUMBER			
(none)			

AT TERMINATION Variable correlated with ACTH	r	n	p
% POSITIVE			
IL2R+ CD3+	.37	20	.054

AT FOLLOW-UP Variable correlated with ACTH	r	n	p
% POSITIVE			
T cell CD2	-.30	21	.095
IL2R+ CD3+	.58	20	.004
CD3+ Transferrin Receptor	.61	20	.002
Leu 2+ DR+	-.32	21	.074
MEAN ABSOLUTE NUMBER			
NK cells leu 4-19+	-.32	21	.080
IL2R+ CD3+	.57	20	.004
CD3+ Transferrin Receptor	-.32	21	.080
Leu 2+ DR+	-.32	21	.080